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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,534	09/01/1999	THOMAS M. KUNDIG	C9015-2007	2743

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,534	KUNDIG, THOMAS M.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 72-91 are pending.

2. In view of the amendment filed 4/16/04, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 80 and 84 stand rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "cytokine assay, an immunoflorescence assay, a tumor growth inhibition assay, tumor size reduction assay, a CTL assay, inhibition of tumor metastasis, increase in life expectancy, infectious disease recovery and observation of the health of the mammal" in Claims 80 and 84 represents a departure from the specification and the claims as originally filed. Said passage has no support in the specification and the claims as originally filed.

Applicants' arguments filed 4/16/04 have been fully considered but are not found persuasive.

Applicants' position is that applicants describe numerous assays useful in detecting a sustained CTL response in the specification at page 11, line 30 through page 13, line 16 and Examples 1-5.

However, the passage pointed out by applicant does not support the term "cytokine assay", immunofluorescence assay, tumor growth assay, tumor size reduction, inhibition of tumor metastasis, increase in life expectancy".

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 79-80, 83, 86, 87, and 90 stand rejected under 35 U.S.C. 102(b) as being anticipated by Grohmann *et al* (J Immunol Methods 137(1): 9-15, March 1991; PTO 892).

Grohmann *et al* teach a method of obtaining a sustained CTL response in a mammal such as mice comprising injecting minute amounts of cell-free antigen such as lysate of highly immunogenic murine lymphoma cells bound to nitrocellulose directly into the lymphatic vessel such as the spleen. The direct injection as taught by Grohmann et al inherently sustained CTL response since the antigen is not being degraded or susceptible to metabolic clearance. Grohmann et al further teach that selected antigen in the reference is capable of inducing CTL response (See entire document). The reference method of injecting antigen directly into the spleen, which is part of the lymphatic system as disclosed on page 73, line 20. The reference method induces cell-mediated immunity (CTL response) such as delayed type hypersensitivity (DTH) response in vivo upon footpad challenge and/or lyses of tumor target cell (chromium release assay) in vitro (See abstract, Materials and methods, in particular). The reference method of delivering the reference antigen is repeated three times at 15-day intervals (See abstract, Materials and Methods, in particular). Grohmann *et al* teach that intrasplenic immunization is useful not only for stimulating the production of antibody but also for the induction of cell-mediated immunity (CTL response) to antigens that can only be obtained in nanograms amount (See page 14, column 2, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 4/16/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) Table I of Grohmann contains from an in vitro assay in which positively selected CD8+ lymphocytes where stimulated in vitro and assayed for cytotoxic activity after 5 days. Table II contains data from a delayed type hypersensitivity assay in which the effect of intrasplenic immunization on the expression of DTH reactivity was measured. Grohmann explicitly acknowledges that DTH reactivity is a cell mediated in vivo response. In contrast to the assay of the instant application which are designed to detect a sustained CTL response and thus measure the presence and duration of CTL with immediately available activity or effector CTL in the animal.

However, the term "measure the presence and duration of CTL with *immediately available activity* or effector CTL in the animal" is not recited in the claim. Further, claim 80 recites the detection step comprises a chromium release assay and CTL assay which are done in

vitro. Further, the reference method of injecting antigen directly in the lymphatic system such as the spleen would inherently induce sustained CTL response.

7. The following are new ground of rejections are necessitate by new reference.

8. Claims 72-74, 77-84, 87, and 89-91 are rejected under 35 U.S.C. 102(b) as being anticipated by Sadao *et al* (translation of Locoregional Immunotherapy-topics at the 13th and 14th Meetings of the Japanese Research Society for Surgical Cancer Immunology, Biotherapy, 9(7): 845-851, 1995; PTO 892).

Sadao *et al* teach a method of obtaining a sustained CTL response in a mammal such as human and experimental animal tumors having cancer by administering an antigen such as OK-432 obtained as a component of a microorganism (acellular) or tumor antigen such as MAGE-I (polypeptide) in lung cancer and melanomas (page 4) by injecting directly into the lymph nodes (See page 13, BRM immunological action, abstract, page 3, in particular) or directly into the lymphatic system such as the spleen (See page 13, BRM immunological action, page 11, last paragraph, in particular) at a level sufficient to induce a CTL response in the mammal against cancers (See pages 8-9, in particular). The reference method of direct injection to the lymph nodes or spleen inherently causes a sustained exposure of the antigen to the mammalian's lymphatic system. The reference antigen is maintained by sustained delivery of the antigen by indwelling reservoir or intermittent replacement administration (See page 11, line 7 from the bottom, in particular). The reference method of detecting the sustained CTL response in the mammal by measuring the reduction in tumor metastasis (see page 13, line 7 from the bottom, in particular) or CTL assay (page 8, in particular). The reference further comprises delivering a cytokine such as IL2, IFN gamma, and/or TNF (See page 13, last paragraph, page 6, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 72, 75-76, and 87-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadao *et al* (translation of Locoregional Immunotherapy-topics at the 13th and 14th Meetings of the Japanese Research Society for Surgical Cancer Immunology, Biotherapy, 9(7): 845-851, 1995; PTO 892) in view of US Pat No. 6,204,250 B1 (of record, March 2001, PTO 892), Coupey *et al* (of record, Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (of record, Immunol Rev 156: 199-209, April 1997; PTO 892).

The teachings of Sadao *et al* have been discussed supra.

The claimed invention as recited in claims 75 and 88 differs from the teachings of the reference only in that the method wherein the antigen is provided in the form of a nucleic encoding the antigen.

The claimed invention as recited in claim 76 differs from the teaching of the reference only in that the method wherein the antigen is provided in the form of a nucleic acid wherein the nucleic acid encoding the antigen comprises a plasmid, a vector or a recombinant viral vector.

The '250 patent, of record, teaches a method of immunizing a mammal such as infant against any target antigen wherein the antigen is delivered in the form of nucleic acid or vector in the host cell that encodes said antigen such as virus or bacteria (See Abstract, column 4, column 7, lines 49-53, claim 14 of '250 patent, in particular). The reference antigen is injected into the infant mammals by any means and route known in the art (See column 8, lines 31-37, in particular). The reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiatior since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline in the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular).

Coupey *et al*, of record, teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the

immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al*, of record, teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antigen as taught by Sadao *et al* for the antigen encoding by nucleic acid as taught by the '250 patent for a method of obtaining sustained CTL response in a mammal as taught by Sadao *et al,* Coupey *et al* and Zinkernagel *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '250 patent teaches that the reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiatior since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular). Coupey *et al* teach that direct injection of antigen to the popliteal lymph node (axillary lymph node) enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

12. Claims 72, 77, 83 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadao *et al* (translation of Locoregional Immunotherapy-topics at the 13th and 14th Meetings of the Japanese Research Society for Surgical Cancer Immunology, Biotherapy, 9(7): 845-851, 1995; PTO 892) in view of US Pat No 5,830,452 A (of record, Nov 1998; PTO 892) and US Pat No 5,279,608 (of record, Jan 1994; PTO 892).

The teachings of Sadao *et al* have been discussed supra.

The claimed invention as recited in claim 77 differs from the teaching of the reference only in that the method wherein the antigen is maintained by sustained, delivery of the antigen using an external device.

The claimed invention as recited in claim 86 differs from the teaching of the reference only in that the method wherein the antigen to the lymphatic system comprises repeated exposure of the antigen to the mammal's lymphatic system.

The '452 patent teach a method of obtaining a sustained CTL response such as enhance anti-tumor efficacy by administering cytokine such as IL-2. The '452 patent teach sustained delivery of any compound of interest using a device external to the mammal such as a computer driven pump (See column 5, lines 57-65, in particular). The reference external device is useful for enhancing the therapeutic index of any compound that is useful to stimulate CTL response such as treating tumors, improving patient compliance and minimizing toxicity (See abstract, in particular).

The '608 patent teaches osmotic pump is suitable for the delivery of any agent such as natural synthetic recombinant peptide, protein, drugs analgesics or combination of agents (See column 6, line 32-35, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made continuously repeated deliver any antigen or drug of interest using a computer driven pump as taught by the '452 patent or osmotic pump as taught by the '608 patent for a method of inducing a sustained CTL response wherein the antigen is maintained by sustained, delivery of the antigen as taught by Sadao *et al,* the '452 patent and the '608 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because he '452 patent teaches the therapeutic index is enhanced due to patient compliance and minimize toxicity (See column 5, lines 57-65, in particular). The '608 patent teaches osmotic pump is suitable for the delivery of any agent such as natural synthetic recombinant peptide, protein, drugs analgesics or combination of agents (See column 6, line 32-35, in particular).

13. Claims 83 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sadao *et al* (translation of Locoregional Immunotherapy-topics at the 13th and 14th Meetings of the Japanese Research Society for Surgical Cancer Immunology, Biotherapy, 9(7): 845-851, 1995; PTO 892) in view of US Pat No 6,037,135

The teachings of Sadao *et al* have been discussed supra.

The claimed invention as recited in claim 85 differs from the teachings of the reference only in that the method wherein the antigen is a patient-matched antigen.

The '135 patent teaches a method of making patient matched antigen such as MHC class I peptide that matches with patient's allele and binds to the TCR for generating the antigen specific cytotoxic T lymphocyte response (See entire document, column 9, line 5-22, in particular). The reference antigen is useful for inducing antigen specific T lymphocytes response in vaccine against tumor and chronic infection (See entire document, column 16, line 62-65, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '135 patent teaches that patient matched antigen is useful for inducing antigen specific T lymphocytes response in vaccine against tumor and chronic infection (See entire document, column 16, line 62-65, in particular).

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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